Progress Report for CTR Grant #786

1. An important goal of this grant was to establish the role of the immune response against lung components in the etiology and pathophysiology of emphysema. We have found that 70% of patients with emphysema that we have tested had antibody titers against denatured collagen. This high incidence has great significance not only in understanding the pathophysiology of the disease but a possible means for early detection of the disease before respiratory symptoms become evident. Copies of the manuscript describing these results are attached.

2. Another important goal of this grant was to examine the hypothesis that aldehydes from cigarette smoke form a complex with lung connective tissue, specifically with collagen. Very early in the course of the investigation, we encountered difficulties in quantitating the titers to collagen-aldehyde complexes. This is because of the low degree of quantitation possible by the hemagglutination technique. We embarked on a program to develop a quantitative and sensitive technique to determine these antibodies. As a result of this investigation, we have developed a radioimmunoassay of collagen which enables us to detect nanogram quantities in the blood. This we consider a significant breakthrough in studies on collagen since collagen was impossible to assay in serum due to interfering substances. We have already started experiments to standardize the reaction between collagen reacted with radioactive formaldehyde and antibodies to collagen and to formaldehyde-collagen complex. This study is covered in the new grant proposal.

3. Experiments on the effect of aldehydes found in the gaseous phase of cigarette smoke on the proliferation rate and biosynthetic activity of lung fibroblasts have been undertaken recently and are described in detail in the proposal (pages 2-4). In short, we have found that minute concentrations of formaldehyde would cause an <u>increase</u> in collagen synthesis which in clinical situations may present as fibrosis. That this indeed is the case was determined by exposure of rats to low levels of formaldehyde. At higher concentrations aldehydes caused a marked decrease in both proliferative activity and biosynthesis of connective tissue. This observation may offer a rational explanation to the pathophysiology of emphysema. If indeed biosynthetic activity of lung fibroblasts is arrested, one would expect to see a slow disappearance of alveolar septal tissue. These experiments, although very exciting, are still in their initial stage and much more work in defining the molecular lesion is required.

4. Using freeze-etching and freeze-fracture techniques, we have characterized the ultrastructure of lung collagen (manuscript attached). We have now moved to the subject of the ultrastructure of lung collagen exposed to cigarette smoke. A smoking machine promised to us by Dr. John Kreisher of the CTR will be of tremendous help in this investigation.

A more complete report on the current status of our projects related to cigarette smoke is incorporated in the new grant proposal.

Supplemental

"A progress report on work that has little bearing on the present application will follow shortly".